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Hypersensitivity pneumonia from the past to the future

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ABSTRACT

Hypersensitivity pneumonia (HP) is an inflammatory and/or fibrotic disease affecting the lung parenchyma and small airways. Exploring the historical context of HP helps to understand how significant changes in risk factors over time have influenced its development. Many inciting agents have been associated with HP since its recognition in 1700. More than 300 etiologic agents have been identified as the cause of the disease. Bacteria, fungi, animal proteins, plant proteins, low molecular weight chemicals, and metals have been identified as inciting agents. New exposures continue to be suspected as causative factors in the development of HP. As occupational and unsalaried avocational practices evolve, give rise to an ever-expanding list of HP-inducing risk factors, including three-dimensional printers (thought to be due to nylon powder used in its manufacture), contaminated home continuous positive airway pressure machines and dental products (methyl acrylates affecting dental technicians).

Keywords: Hypersensitivity pneumonia, etiologic agents, new exposures

INTRODUCTION

Hypersensitivity pneumonia (HP) is an inflammatory and/or fibrotic disease affecting the lung parenchyma and small airways. It is typically caused by an immune-mediated reaction triggered by an overt or covert inhaled antigen in susceptible individuals. HP has historically been termed extrinsic allergic alveolitis.[1] Knowing the historical development of HP not only helps to understand which antigens cause it but also helps to understand how significant changes in risk factors over time have influenced the development of HP. The history of this disease is largely uncertain. Some case reports claim that the disease can be traced back to the 18th century or earlier. Later reports and investigations suggest that the disease is a relatively modern construct, dating back only to the early 20th century.[2] Respiratory diseases in agricultural workers were described in the early 16th century. Bernardino Ramazzini (1633-1714), in his book 'De Morbis Artificium Diatriba' (Diseases of Labourers), stated that almost everyone who earned a living by sifting or measuring grain had shortness of breath, cachexia and rarely reached old age. Despite the long-standing recognition of agricultural lung diseases, the first clear clinical report of HP was in 1932, when the British physician Munro Campbell, in Westmorland during a particularly damp hay-making season, also clearly describes at least five cases in farm workers who developed dyspnea, mild fever, and dry wheezing on examination.[3] WN Pickles,[4] describing a series of several farmers who developed similar symptoms and chest radiographic appearances after working with moldy hay and whose symptoms subsided when exposure was avoided, stated that it should be called farmer's lung. Although farmers' lung remain one of the HP classes, its incidence has decreased over time. This decline is thought to be due to changes in farming practices. The first definitive report of HP in birds was described in 1965 by Reed et al.[5] reported three cases of young male pigeon breeders who developed a febrile illness and a fine diffuse interstitial pneumonia on chest radiographs, all of which cleared after avoidance of exposure and returned upon prevocational re-challenge. The evolution in manufacturing during post-World War II industrialization led to new exposures and irritants. Following the large-scale use of isocyanates in the production of polyurethane resins for flexible foam, synthetic rubber, adhesives, and paints, a series of four cases of patients with isocyanate-associated HP was described in 1976.[6] As industrialization after World War II increased the use of mechanization, the use of metalworking fluids also increased. A wide range of metalworking fluids are used for cooling and lubrication purposes in a variety of applications with varying properties and chemical compositions. Such metalworking contaminants, recirculated and aerosolized under high pressure, caused the first described outbreaks of so-called 'machine operator's lung' in the 1990s.[7]

EPIDEMIOLOGY

The prevalence and incidence of HP varies greatly depending on the intensity of exposure, geographical area, and local

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climate.[8] Most of the epidemiological information on HP has been obtained from studies of farmers and bird breeders. In mild clinical or subclinical cases, the diagnosis of HP may be missed and misdiagnosed as viral disease or asthma. Both of these diseases may have non-specific clinical signs mimicking HP. In a study, the one-year prevalence rate of the disease was determined as 1.67-2.71 (11.2% over 65 years old) per hundred thousand people, half of the cases were evaluated as chronic hypersensitivity pneumonia.[9] In the United Kingdom, the incidence was found to be 0.9 per 100,000 people in the period 1991-2003.[8] Farmer's lung is one of the most common forms of HP, affecting 0.4 to 7 percent of the farming population.[10-14] The reported prevalence of HP among bird fanciers is even more variable than farmer's lung; estimates range from 20 to 20,000 affected individuals per 100,000 persons at risk.[15,16]

ETIOLOGIC AGENTS

HP is a syndrome involving the lung parenchyma and specifically the alveoli, terminal bronchioles, and alveolar interstitium due to a delayed allergic reaction. This reaction occurs secondary to repeated and prolonged inhalation of different types of organic dusts or other substances to which the patient is hypersensitive, especially organic dusts of animal or vegetable origin, less commonly chemicals.[17] More than 300 etiologic agents have been identified as the cause of the disease.[18] Many inciting agents have been associated with HP since its recognition in 1700, but antigen and exposure were not identified in up to 60% of HP patients despite an extensive history.[1] The most common forms are bird fancier's disease and farmer's lung.[19] The main source of antigens in the farmer's lung is the proliferation of thermophilic actinomycetes in straw or dust with high humidity and temperatures between 40 and 60˚C.[20] Bird or pigeon breeder's lung disease is caused by exposure to antigens in the faeces of birds. Indirect exposure from feather beds or down duvets has also been reported to cause the disease. Due to the change in working conditions in industrialized countries, the prevalence of farmer's lung decreased but HP cases due to metalworking fluids increased.[21]

NEW EXPOSURES CAUSATIVE FACTORS

New exposures continue to be suspected as causative factors in the development of HP. Central to their identification are a pattern as consistently described in the literature; symptom onset when in the presence of an exposure; improvement with avoidance; recurrence upon inhalational rechallenge; typical radiographic imaging, histopathological findings, and, in some reports, positive precipitins. As occupational and unsalaried avocational practices evolve, the application of these criteria gives rise to an ever-expanding list of HP-inducing risk factors, including three-dimensional printers (thought to be due to nylon powder used in its manufacture), contaminated home continuous positive airway pressure machines and dental products (methyl acrylates affecting dental technicians).[2]

CATEGORIZATION

For many years, the clinical forms of HP have been categorized as acute, subacute, or chronic, depending on the duration and intensity of exposure and the duration of the disease. However, this categorization has not been satisfactory due to the great variability and overlap in the clinical course of HP. Acknowledging the limitations of the previous classification system, the 2020 guidelines prepared by the American Thoracic Society, the Japanese Respiratory Society, and the Latin American Thoracic Society (ATS/JRS/ALAT) classified HP into non-fibrotic (purely inflammatory) and fibrotic (inflammatory+fibrotic or purely fibrotic) phenotypes based on the predominant presence or absence of fibrosis on imaging or histopathological examination.[1] It is accepted that the presence of fibrosis is a critical determinant of prognosis.

CLINICAL FEATURES

Common HP symptoms include dyspnea and cough. Less frequent symptoms are chest tightness and constitutional symptoms, such as fever, chills, weight loss, and malaise. Symptom onset varies, ranging from acute (days to weeks), insidious (months to years), or recurrent episodes. Acute symptoms, potentially with systemic signs, are more typical in nonfibrotic HP, while an insidious onset is often seen in fibrotic HP.[22]

CLINICAL ASSESSMENT

Diagnosis is not easy because there is no gold standard diagnostic test in HP. The diagnosis is based on determining exposure to a causative agent and excluding other possible interstitial lung diseases. The diagnosis is based on the integration of a number of factors including exposure history, detection of precipitating antibodies, clinical features, bronchoalveolar lavage, radiology, and pathology.[23,24] The diagnosis of HP should be made with a multidisciplinary approach. Fibrotic HP should be considered in the differential diagnosis of all patients with fibrotic interstitial lung disease. It is difficult to differentiate this group of patients because exposures cannot be determined in almost half of the patients with fibrotic HP. In non-fibrotic HP, the diagnosis may be easier since the exposure can usually be easily detected. The ATS/JRS/ALAT guidelines emphasize the importance of three main points for HP diagnostic criteria. These are identification of exposure (clinical history with or without questionnaire, serum IgG test against potential antigens associated with HP), radiological pattern, and lymphocytosis/histopathological findings in bronchoalveolar lavage (BAL). Diagnostic algorithms have been developed to minimize invasive interventions.[1]

TREATMENT

Antigen avoidance is the cornerstone of treatment for symptomatic HP and usually results in regression of disease.[20] Additional treatment may be required in more severe or progressive disease. The best-studied forms of HP are farmer's lung and bird fancier's lung; treatment of other types of HP largely is extrapolated from the experiences in these populations. Corticosteroids and immunosuppressive drugs can be used in pharmacological treatment. Recently, antifibrotic treatments can be used depending on HP phenotypes. Lung transplantation may be considered in patients with severe clinical and functional loss.[25]

PROGNOSIS

The long-term outcome of HP varies and depends on factors such as the specific causal antigen, duration of antigen

exposure, and host response. Patients with acute HP who have complete avoidance of the causal antigen tend to experience near-total recovery of lung function, although full recovery may take several years after the inciting exposure ceases.[24,26] Bird fancier's HP appears to have a worse prognosis than farmer's lung. The prognoses of other varieties of HP are less well described. In general, patients with evidence of pulmonary fibrosis on surgical lung biopsy have a poorer prognosis than those without such changes.[27]

CONCLUSION

History can teach us a lot about HP, but there is still much to learn. Suffice it to say that exposures not previously known to cause HP will continue to be discovered over time. Looking back and being vigilant going forward can help us reduce the risk of HP in the years to come.

ETHICAL DECLARATIONS

Referee Evaluation Process

Externally peer-reviewed.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

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Author Contributions

All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

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